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(54) Title: INTRAVASCULAR POLYMERIC STENT

(57) Abstract

The invention relates to an intravascular polymeric stent manufactured from an amorphous, biocompatible polymer.

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Title: Intravascular polymeric stent

The invention relates to an intravascular polymeric stent, more particularly to a stent which is manufactured from a biocompatible, non-thrombogenic material. Stents are (spiral) bodies suitable for maintaining the patency of veins in the human body, more particularly veins which have undergone a so-called Dotter treatment.

In the 1960s Charles Dotter introduced a technique for treating obstruction of coronary arteries (stenosis), which is generally the result of atherosclerosis. This treatment is presently known as the so-called Dotter therapy, a promising and widely accepted alternative to bypass surgery. Important disadvantages of this technique are acute collapse, chronic complete occlusion and restenosis of the affected vessels.

In order to obviate these problems, an intravascular stent can be placed in the treated segment of the vessels in order to maintain patency. The first stents were described in 1969 and consisted of a tubular stainless steel coil spring. Thereafter a large number of other designs, substantially consisting of metal, were developed.

The metal stents currently in use can be divided into two types, based on the manner of placement, viz. self-expanding or balloon-expanding.

These metal stents have been particularly successful in preventing restenosis, but it is to be expected that complications can occur in the long term. Metal stents are far from ideal, since metals are relatively thrombogenic and non-degradable. Moreover, metal stents may perforate the walls of the blood vessel.

An ideal stent, on the other hand, would be compatible in the biological system, i.e. compatible with blood, non-thrombogenic, not inducing any rejection reactions, and biodegradable, while any decomposition products would not be toxic.

The literature describes degradable intravascular stents which are manufactured from poly(L-lactide). Poly(L-lactide) is a hydrolytically labile semi-crystalline aliphatic

polyester which is used in a large number of biomedical applications since the degradation product thereof, L-lactic acid, possesses a very minor toxicity. Recent developments, however, have shown that implantation of semi-crystalline poly(L-lactide) may eventually lead to a late tissue reaction because of the presence of small highly crystalline low-molecular poly(L-lactide) particles which are hydrolytically rather stable. These particles can be found at the site of implantation up to 5 years after implantation.

The object of the invention is to provide an intravascular stent suitable for use in blood vessels after a Dotter therapy, which does not have the disadvantages of the above-described materials.

According to the invention, such an intravascular stent is manufactured from an amorphous, biocompatible polymer. Surprisingly, it has been found that amorphous biocompatible polymers are highly suitable for the manufacture of stents, without possessing the disadvantages of, for instance, the semi-crystalline poly(L-lactide).

A next advantage of such a polymeric stent resides in the fact that the material, after the cure of the blood vessel, which takes about three weeks, is absorbed by the body, since the material has no further function anymore.

The stent can be implanted in the blood vessel by a catheter as an elongated spiral of slight diameter. The stent is then thermally expanded to its original spiral shape. To make this possible, the polymeric material should have a glass transition temperature just below the body temperature. The material of the stents should therefore have a so-called thermal shape memory. A suitable stent can be manufactured by the *in situ* polymerization of suitable starting materials in a spiral-shaped matrix, for instance manufactured from PTFE. After polymerization, the spiral obtained can be stretched to any desired shape above the glass transition temperature of the material. This shape can be frozen after cooling to a temperature below the glass transition temperature. This makes it possible to introduce the stent into the blood vessel via a

catheter. After the stent has been introduced into the blood vessel, it can expand freely to the original spiral shape at body temperature. The closer to the body temperature the T_g of the polymeric material is, the faster the material will resume its original shape again. The expanding spiral then anchors itself in the blood vessel by exerting pressure on the wall of the blood vessel. It is therefore preferred to use a material which has a T_g between 0°C and 37°C.

In such situations, creep resistance is a particularly important property because it should be possible for the elongated spiral to expand completely to its original dimensions upon heating. A permanent deformation as a result of the elongation of the coil spring is undesirable. It has been found, however, that the use of polymeric (amorphous) networks as stent material gives an article of sufficient creep resistance. In practice this means that the creep of the material at body temperature is nil.

According to the invention, a large number of plastics are suitable for the manufacture of the polymeric stent. The common feature of these polymers is that they are amorphous, cross-linked biologically active polymers, which are preferably also biodegradable. Examples of suitable groups of polymers are the amorphous non-crystallizable polylactic acid networks, the highly cross-linked polyurethane networks, which also includes the conversion products of star prepolyesters, for instance based on lactic acid copolymers, with diisocyanate. The extent of cross-linking should be such that the maximum gel content is obtained. Preferably, no unreacted low-molecular components are present.

These polymers moreover have in common that they are sterilizable in the conventional manner with steam and that they meet the biocompatibility requirements given in the introduction (compatible with blood, non-thrombogenic, not causing any rejection reactions, biodegradable, while any decomposition products are non-toxic).

The first group of polymers, amorphous non-crystallizable polylactic acid networks, comprises inter alia

the amorphous copolymers of lactides and glycolides, which have been converted to a network with suitable cross-linking agents. In view of the nature of the materials, cross-linking for the purpose of forming a network is preferably effected with a tetra- or higher functional cyclic ester, preferably with a tetrafunctional cyclic cross-linking agent such as biscaprolactone.

The second group of polymers, highly cross-linked polyurethane networks, is described inter alia in International patent application PCT/NL93/00203 filed 13 October 1993.

This group of polymers consists of cross-linked polyurethane networks obtainable by reacting one or more low-molecular polyols with a functionality of three or more and one or more polyisocyanates with a functionality of two or more in the absence of a solvent.

For obtaining suitable materials it is of importance that the polyols are low-molecular. In practice this means that the equivalent weight of the polyol is preferably 125 at a maximum. 'Equivalent weight' in this case is understood to mean the molecular weight per hydroxyl group. In general, the starting material is 3 or 4 functional polyols, although higher functionalities can be used as well. Practically, an upper limit lies at a functionality of 8. It is also possible, however, to include a minor amount of diols in the mixture. However, since diols do not give rise to cross-linking, either the amount thereof should be kept low or one should work with substantially 3 or higher functional isocyanates. In general, the number of hydroxyl groups coming from a diol will be less than about 10% of the total number of hydroxyl groups.

Preferred polyols are selected from the group consisting of triethanolamine (TEA), tri-isopropanolamine, 1,1,1,-trimethylol-propane (TMP), N,N,N',N'-tetrakis (2-hydroxypropyl)-ethylenediamine (Quadrol), octakis(2-hydroxypropyl) penta-erytrytyltetra-amine, tetrakis{β-hydroxyethyl}methane, 1,1,1 trihydroxyethylpropane, 1,1,1 trihydroxyethylethane and other polyols. It is also

possible to use modified or unmodified pentaerytritol or inositol.

The polyisocyanates which can be used according to this embodiment of the invention are the conventional diisocyanates and higher isocyanates, for instance selected from the group consisting of butanediisocyanate, hexamethylene diisocyanate, dodecane diisocyanate, trans 1,4-cyclohexane diisocyanate, methylene dicyclohexane diisocyanate, lysine di- or triisocyanate, isophorone diisocyanate, p-phenylene diisocyanate, methylene diphenyl diisocyanate, triphenyl-methanetriisocyanate, thiophosphoric acid tris(4-isocyanatiphenyl ester), polymeric methylene diphenyl diisocyanate as well as trimerization products and adducts of these isocyanates, for instance based on polyols. Examples of suitable polyols have been given hereinabove.

The third product group comprises the conversion products of star prepolyesters and a di-isocyanate, preferably a di-isocyanate based on an L-lysine derivative or on 1,4-diisocyanatobutane. A number of these products are described inter alia in International patent application PCT/NL 88/00060, incorporated herein by reference.

According to this variant of the invention, as diisocyanate, preferably a lysine derivative is used having one of the formulae 1-3 of the sheet of formulae, or 1,4-diisocyanatobutane. These isocyanates are reacted with suitable polyols, such as polyester polyols based on lactide, glycolide, and/or lactones such as ε-caprolactone or δ-valerolactone. Such a polyester can be initiated with a suitable low-molecular polyol, such as glycol, pentaerytritol, myo-inositol and the like.

In the case where it is desirable that the material of the polymeric stent is broken down in the body, it is preferred to manufacture the polymer from polymers whose decomposition products are not toxic.

Although the three groups of polymers described hereinabove are highly suitable as such, it may be desirable, in order to obtain the desirable strength properties, that a

second phase be incorporated into the material, for instance by the introduction of one or more fillers, fibers and/or a second polymeric phase. In particular by incorporating a second polymeric phase, in the form of a separate rubber phase, materials are obtained which possess a particularly good combination of mechanical properties.

The invention will now be elucidated in and by a few examples which should not be construed as limiting.

Example 1

Cross-linked poly(lactide-ε-caprolactone;80/20 mole ratio) was manufactured by *in situ* polymerization in a spiral-shaped PTFE mold. The monomer mixture, the cross-linking agent (5,5'-bis(oxepan-2-one)) and the catalyst, tin octoate (monomer-catalyst ratio 1000 based on weight) were introduced into a silanized glass ampoule and melted and homogenized at 130°C. Then the mold, also disposed in the ampoule, was filled with the molten mixture by allowing it to fill up under the influence of gravity. The polymerization was carried out at 130°C for 90 hours. Upon completion of the polymerization the stent obtained could easily be removed from the mold.

Example 2

A stent was manufactured from a highly cross-linked polyurethane network, using a PTFE mold. The starting materials, triethanolamine, tetrakis(2-hydroxypropyl)-ethylenediamine and hexamethylenediisocyanate, were purified by distillation at reduced pressure. The components were then mixed and degassed a number of times. With a syringe the mixture was introduced into the mold and gelled at room temperature. Then curing was allowed to take place for 24 hours at about 100°C, whereafter the stent was removed from the mold.

Results

The mechanical properties of a number of stents manufactured according to Examples 1 and 2 are included in the following table and figures.

Table 1

mechanical properties of polyester and polyurethane networks at different temperatures

	T	Tensile strength	Young's modulus	elongation at break	toughness	T_g
	°C	MPa	MPa	%	MPa	°C
1	40	21	21	450	25	32
2	40	17	57	96	7	23
3	24	60*	1200	26	14	70
4	80	10	21	50	2	70
5	80	10	21	50	2	73

1: poly(lactide-co-ε-caprolactone), 80/20 mole %, cross-linked with 5,5'-bis(oxepan-2-one)

2: TEA/Quadrol(40:60)/HDI PU network after water uptake

3,4: TEA/Quadrol(40:60)/HDI PU network

5: TEA/Quadrol(20:80)/HDI PU network

*: Yield stress:71 MPa

CLAIMS

1. A polymeric stent manufactured from an amorphous, biocompatible and cross-linked polymer.

2. A stent according to claim 1, manufactured from a polymer having a shape memory at body temperature.

3. A stent according to claim 1 or 2, manufactured from a polymer selected from the group consisting of amorphous, non-crystallizable polylactic acid networks, highly cross-linked polyurethane networks and conversion products of star prepolyesters and di-isocyanate.

4. A stent according to claim 2, manufactured from polylactide copolyester cross-linked with a di-functional cyclic ester.

5. A stent according to claim 4, manufactured from a poly(lactide-ε-caprolactone) cross-linked with biscaprolactone.

6. A stent according to claim 3, manufactured from a polyurethane network obtained by polymerizing a suitable polyol, preferably a triol or a tetra-ol and a suitable polyisocyanate, preferably a diisocyanate, in the absence of solvents.

7. A stent according to claims 1-6, manufactured from a polyphase polymer.

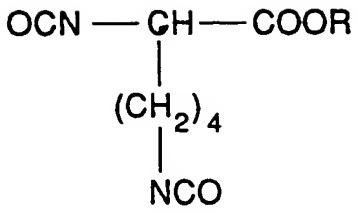
8. A stent according to claim 7, manufactured from a polymer comprising one or more fillers, fibers and/or a second, preferably amorphous, polymeric phase.

9. A biomedical aid manufactured from an amorphous, biocompatible and cross-linked polymer having a shape memory at body temperature.

10. A method for manufacturing a stent or a biomedical aid according to claims 1-9, comprising polymerizing the starting materials for the polymer in a spiral-shaped mold, followed by removing the obtained article from the mold.

11. A method according to claim 10, wherein the mold is manufactured from polytetrafluoroethene.

1



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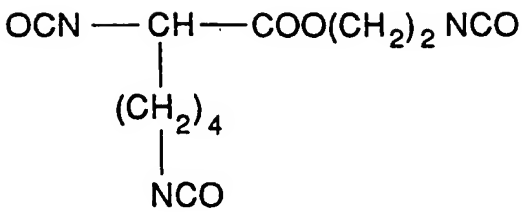

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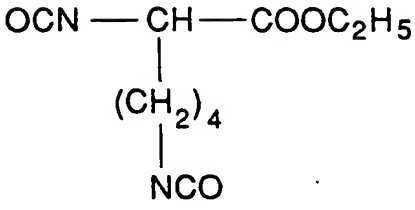

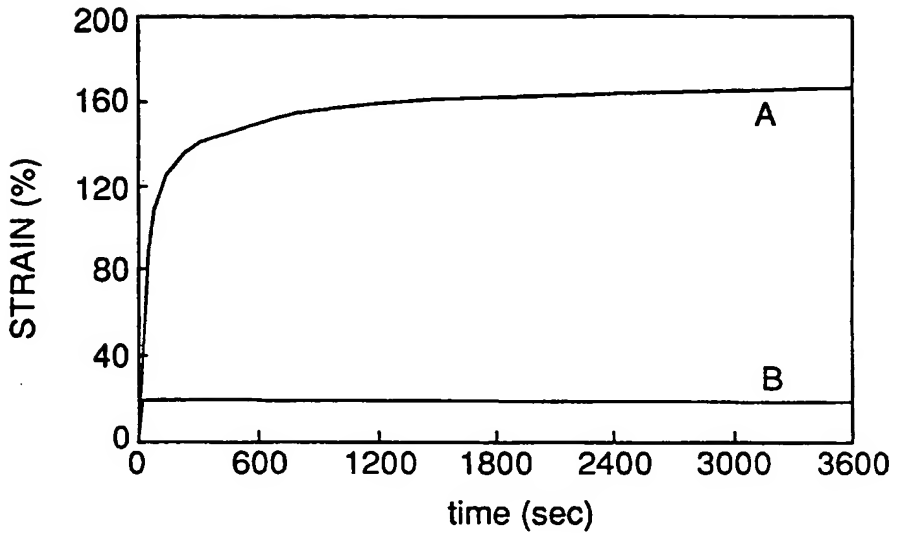

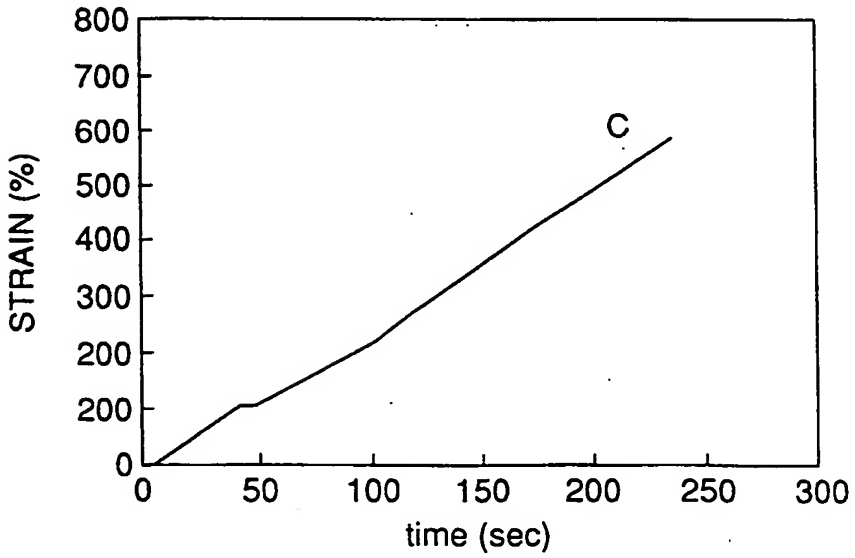

FIG.1 Creep behavior at 40°C of:

a) cross-linked poly (lactide-*co* -ε-caprolactone) (80:20 mole %) (σ=1.5 MPa)

b) highly cross-linled polyurethane (σ=2.5 MPa)

c) Linear poly(lactide-*co* -ε-caprolactone) (50:50 mole %) (σ=3.5 MPa)

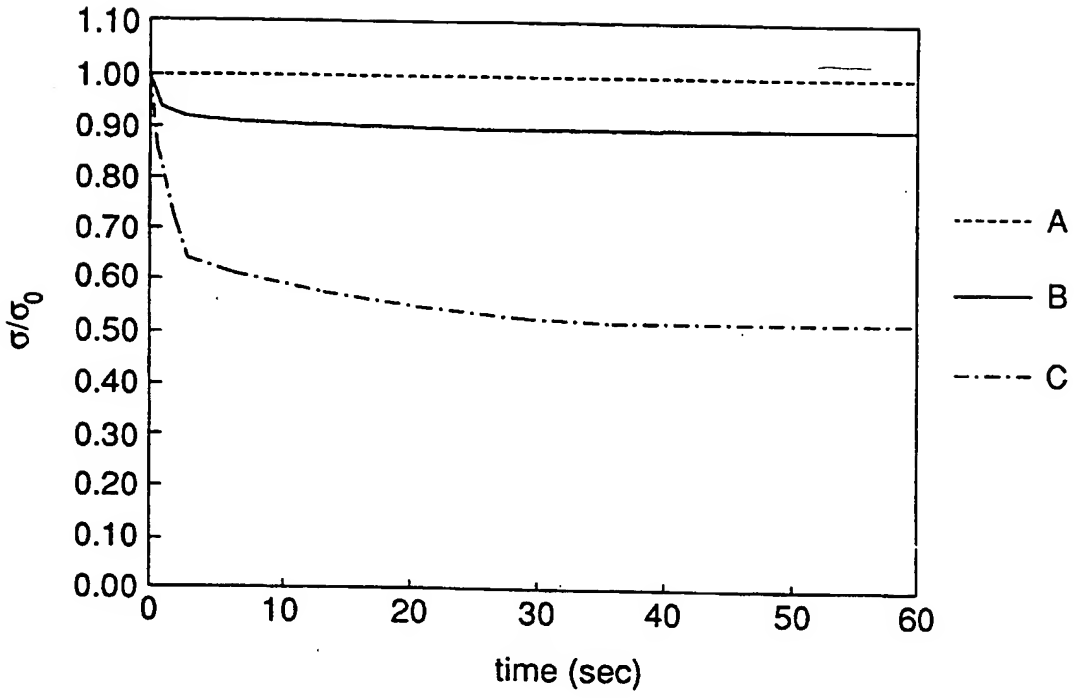

FIG.2 Strain relaxation on of spiral stents at 40°C of:
a) highly cross-linked polyurethane
b) cross-linked poly(lactide-*co* -ε-caprolactone) (80:20 mole %)
c) Linear poly(lactide-*co* -ε-caprolactone) (50:50 mole %)
(σ_0 was about 0.1 MPa)

INTERNATIONAL SEARCH REPORT

Inter. .onal Application No
PCT/NL 95/00122

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L31/00 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 326 426 (JAPAN MEDICAL SUPPLY CO.,LTD) 2 August 1989 see claims ---	1,2
X	WO,A,93 15787 (CHANDLER, JERRY, W.) 19 August 1993 see claims ---	1,3
X	WO,A,92 04393 (RIJKSUNIVERSITEIT TE GRONINGEN) 19 March 1992 see claims; examples ---	1,3
X	WO,A,89 05830 (STICHTING BIOMAT.) 29 June 1989 cited in the application see the whole document --- -/--	1,3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 May 1995	15. 06. 95

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Inter. .onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BIOMATERIALS, vol.14, no.14, November 1993 pages 1089 - 1097 P. BRUIN ET AL. 'AUTOCLAVABLE HIGHLY CROSS-LINKED POLYURETHANE NETWORKS IN OPHTHALMOLOGY.' see the whole document	1-11
Y	EP,A,0 460 439 (AMERICAN CYANAMID COMPANY.) 11 December 1991 see examples	1-11
Y	EP,A,0 420 541 (BRISTOL-MYERS SQUIBB CO.) 3 April 1991 see claims	1-11
A	EP,A,0 428 479 (SCHNEIDER (EUROPE) AG.) 22 May 1991	1-11

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INTERNATIONAL SEARCH REPORT

information on patent family members

Intn. .onal Application No
PCT/NL 95/00122

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0326426	02-08-89	JP-A-	1192367	02-08-89
		DE-D-	68920055	02-02-95
		US-A-	4950258	21-08-90
WO-A-9315787	19-08-93	NONE		
WO-A-9204393	19-03-92	NL-A-	9001984	01-04-92
		AU-B-	649488	26-05-94
		AU-A-	8658891	30-03-92
		CA-A-	2091342	11-03-92
		EP-A-	0548237	30-06-93
		JP-T-	6501045	27-01-94
WO-A-8905830	29-06-89	NL-A-	8703115	17-07-89
		EP-A-	0417095	20-03-91
EP-A-0460439	11-12-91	US-A-	5080665	14-01-92
		AU-B-	652761	08-09-94
		AU-B-	8034794	16-02-95
		CA-A-	2046192	07-01-92
		US-A-	5324307	28-06-94
		US-A-	5342395	30-08-94
		US-A-	5376102	27-12-94
EP-A-0420541	03-04-91	US-A-	5085629	04-02-92
		AU-B-	633361	28-01-93
		AU-A-	6364390	11-04-91
		CA-A-	2025626	28-03-91
		JP-A-	3205059	06-09-91
EP-A-0428479	22-05-91	AT-T-	114233	15-12-94
		AU-B-	640422	26-08-93
		AU-A-	6574190	09-05-91
		CA-A-	2028897	02-05-91
		DE-U-	9014845	10-01-91
		DE-D-	59007761	05-01-95
		ES-T-	2063325	01-01-95
		JP-A-	3155869	03-07-91
		US-A-	5147385	15-09-92